INT J TUBERC LUNG DIS 25(3):182–190

http://dx.doi.org/10.5588/ijtld.20.0778

Unhealthy alcohol use independently associated with unfavorable TB treatment outcomes among Indian men

S. R. Cox,[1] A. N. Gupte,[1] B. Thomas,[2] S. Gaikwad,[3] V. Mave,[1,4] C. Padmapriyadarsini,[2] T. R. Sahasrabudhe,[5] D. Kadam,[3] N. Gupte,[1,4] L. E. Hanna,[2] A. Kagal,[3] M. Paradkar,[1,4,6] K. Thiruvengadam,[2] D. Jain,[4] S. Atre,[1,5,6] K. Sekar,[2] S. Raskar,[1,4,6] S. V. B. Y. Shivakumar,[1,6] R. Santhappan,[2] S. Deshmukh,[1,4,6] N. Pradhan,[1,4,6] V. Kulkarni,[1,4,6] A. Kakrani,[5] M.S. Barthwal,[5] T. Sawant,[5] A. DeLuca,[1] N. Suryavanshi,[1,4,6] G. Chander,[1] R. Bollinger,[1] J. E. Golub,[1] A. Gupta[1]

[1]Johns Hopkins University (JHU), School of Medicine, Baltimore, USA; [2]National Institute of Research in Tuberculosis (NIRT), Chennai, [3]Byramjee Jeejeebhoy Government Medical College (BJGMC) and Sassoon General Hospital, Pune, [4]BJGMC Clinical Research Site, Pune, [5]Dr DY Patil Medical College Hospital and Research Centre, Dr DY Patil Vidyapeeth, Pune, [6]Johns Hopkins India Private Limited, Pune, India

SUMMARY

BACKGROUND: Approximately 10% of incident TB cases worldwide are attributable to alcohol. However, evidence associating alcohol with unfavorable TB treatment outcomes is weak.

METHODS: We prospectively evaluated men (≥18 years) with pulmonary TB in India for up to 24 months to investigate the association between alcohol use and treatment outcomes. Unhealthy alcohol use was defined as a score of ≥4 on the Alcohol Use Disorders Identification Test-Concise (AUDIT-C) scale at entry. Unfavorable TB treatment outcomes included failure, recurrence, and all-cause mortality, analyzed as composite and independent endpoints.

RESULTS: Among 751 men, we identified unhealthy alcohol use in 302 (40%). Median age was 39 years (IQR 28–50); 415 (55%) were underweight (defined as a body mass index [BMI] <18.5 kg/m^2); and 198 (26%) experienced an unfavorable outcome. Unhealthy alcohol use was an independent risk factor for the composite unfavorable outcome (adjusted incidence rate ratio [aIRR] 1.47, 95% CI 1.05–2.06; $P=0.03$) and death (aIRR 1.90, 95% CI 1.08–3.34; $P=0.03$), specifically. We found significant interaction between AUDIT-C and BMI; underweight men with unhealthy alcohol use had increased risk of unfavorable outcomes (aIRR 2.22, 95% CI 1.44–3.44; $P<0.001$) compared to men with BMI ≥18.5 kg/m^2 and AUDIT-C <4.

CONCLUSION: Unhealthy alcohol use was independently associated with unfavorable TB treatment outcomes, highlighting the need for integrating effective alcohol interventions into TB care.

KEY WORDS: mortality; failure; recurrence; adverse outcomes; AUDIT

TB is the number one infectious cause of death worldwide, accounting for over 1.4 million deaths annually.[1] Much attention has been focused on HIV and more recently, on smoking, diabetes and undernutrition as risk factors for adverse TB treatment outcomes, but relatively little attention has been paid to alcohol. Alcohol consumption is a well-described risk factor for developing TB disease, with approximately 10% of incident TB cases worldwide attributable to alcohol.[2–4]

India has the world's largest burden of TB, with over 2.6 million cases reported in 2019, which accounted for 26% of all cases globally.[1] India's strategic plan for TB cites management of comorbidities, including alcohol dependence, as a key strategy for improving treatment success.[5] Alcohol use is on the rise in India, with alcohol per capita consumption increasing by 3.3 L from 2005 to 2016.[6,7] Among men, prevalence of alcohol use disorders doubled in just 5 years (4.5% in 2010 to 9.1% in 2016).[7,8] Several studies have demonstrated that alcohol use is high among patients with TB; 25–55% of Indian patients with TB are estimated to have unhealthy alcohol use.[9–15]

Considering India's high TB burden and recent rise in alcohol consumption, it is critical to study the association between alcohol use and TB treatment outcomes in this context. A recent systematic review found that less than 20% of studies of alcohol and TB

* BT, SG, VM, CP, TRS, and DK contributed equally to this manuscript.

Correspondence to: Samyra R Cox, Johns Hopkins University, School of Medicine, Division of Infectious Diseases, Center for Clinical Global Health Education, 600 North Wolfe Street, Phipps 521, Baltimore, MD 21287, USA. email: scox26@jhmi.edu

Article submitted 12 October 2020. Final version accepted 4 December 2020.

outcomes used high-quality definitions for alcohol use. Furthermore, studies from TB-endemic settings were underrepresented, and few studies adjusted for important confounders such as low body mass index (BMI).[16] Studies from TB-endemic settings using validated epidemiological tools for measuring alcohol exposure and its association with TB treatment outcomes, independent of comorbidities, are therefore urgently needed.

To address this gap in the literature, we used the validated Alcohol Use Disorders Identification Test-Concise (AUDIT-C) scale to determine whether unhealthy alcohol use was independently associated with unfavorable TB treatment outcomes among men with drug-susceptible pulmonary TB (PTB) in well-defined longitudinal cohorts in India.[17]

METHODS

Study design and population

We pooled data from two prospective cohort studies in India—Cohort for TB Research by the Indo-US Medical Partnership (CTRIUMPh) and the Impact of Diabetes on TB Treatment Outcomes (TBDM) study conducted at the Byramjee Jeejeebhoy Government Medical College (BJGMC) and Dr DY Patil Vidyapeeth, both in Pune, and the National Institute for Research in Tuberculosis (NIRT) in Chennai, India.[18,19] Both studies followed similar protocols for TB case recruitment, systematic follow-up, alcohol use classification and outcome assessment. From December 2013 to November 2018, adults ($\geq$18 years) with microbiologically confirmed or clinically suspected PTB were enrolled within 1 week of treatment initiation. Participants with multidrug-resistant TB (MDR-TB) or HIV were excluded (TBDM study only). All participants received TB treatment in accordance with India's standard guidelines.[20] We assessed outcomes during treatment and up to 18 months following treatment completion.

Definitions

At entry, we administered the standardized AUDIT-C questionnaire, which has been validated in India.[21] The AUDIT-C is a three-item questionnaire with scores ranging from 0 to 12 points. Individuals with AUDIT-C $\geq$ 4 were categorized as having unhealthy alcohol use. This cut-off was shown to have optimal sensitivity and specificity based on a prior validation study.[22]

Unfavorable TB treatment outcomes included failure, recurrence or death. Treatment failure was defined as testing positive for TB on sputum microscopy or culture during the last 2 months of treatment. TB recurrence was defined as testing positive for TB on sputum microscopy or culture following successful treatment completion. Death was defined as all-cause mortality within 24 months of treatment initiation.

Detailed clinical and sociodemographic data were collected at baseline. Severely underweight was defined as having a BMI of $<$16.5 kg/m^2, underweight as BMI 16.5–18.4 kg/m^2, normal weight as 18.5–24.9 kg/m^2, and overweight as BMI $>$25 kg/m^2.[23] Diabetes was defined as glycated hemoglobin (HbA1c) $>$6.5%, or random blood glucose $>$200 mg/dL before physician diagnosis. Smoking was defined as current or previous use of tobacco. Participants with monthly household income less than INR5000 ($\sim$USD70) were considered to be living in poverty.[24] A participant lost to follow-up (LTFU) was defined as incomplete treatment, $>$2 consecutive visits missed, and unreachable.

Statistical analysis

Given the very low prevalence of unhealthy alcohol use among women in these cohorts ($<$1%) (Supplementary Figure S1), our analyses were restricted to men. Our primary exposure of interest was unhealthy alcohol use (AUDIT-C $\geq$ 4) measured at TB treatment initiation. Any alcohol consumption and AUDIT-C as a continuous variable were assessed as secondary exposures. The primary endpoint of interest was a composite unfavorable TB treatment outcome of failure, recurrence or all-cause death. Each individual was only assigned one outcome (first outcome experienced). Secondary endpoints of interest included failure, recurrence, or all-cause death analyzed as independent endpoints.

As part of our exploratory analysis, we assessed group-wise differences in unhealthy alcohol use by baseline characteristics using Fisher's Exact and Wilcoxon rank-sum tests. Incidence rates for outcomes were calculated as the total number of participants who experienced at least one unfavorable outcome divided by total person-time at risk per 100 person-years (py); 95% confidence intervals (CIs) were based on quadratic approximation to Poisson distribution.

For our primary analysis, we conducted uni- and multi-variable negative binomial regression, accounting for over-dispersion of outcome distribution, to measure the association between unhealthy alcohol use and the composite unfavorable outcome.[25] We used person-time at risk as an offset in the regression analyses, and reported incident rate ratios (IRRs) visualized using forest plots. We accounted for potential confounders identified a-priori based on literature review (age, BMI, socio-economic status, smoking, smear grade) and by exploratory data analysis (location). We also assessed interaction with low BMI, reported in the literature as a risk factor for unfavorable TB treatment outcomes.[26,27] Data were analyzed using Stata v14.2 (StataCorp, College Station, TX, USA).

Ethical approval

The CTRIUMPh and TBDM studies were approved by the Institutional Review Boards at each participating institution (Johns Hopkins University, Baltimore, MD, USA; NIRT, Chennai, India; BJGMC and Dr DY Patil Vidyapeeth, both Pune, India). All participants provided written informed consent.

RESULTS

Baseline characteristics and alcohol use

Among 751 men, median age was 39 years (IQR 28–50), 581 (77%) were enrolled in Pune, 415 (55%) were underweight (BMI <18.5 kg/m^2), and 270 (36%) were ever-smokers; 226 (30%) men had fewer than 5 years of education and 113 (15%) were living in poverty; 526 (70%) were AFB smear-positive and 677 (90%) were AFB culture or Xpert® MTB/RIF (Cepheid, Sunnyvale, CA, USA) confirmed (Table 1).

Of the 751 men recruited, 407 (54%) men reported ever consuming alcohol, and prevalence of unhealthy alcohol use at entry was 40% ($n = 302$) (Table 1, Supplementary Table S1). Men with unhealthy alcohol use tended to be older, with a median age of 42 years (IQR 32–50), compared to those with AUDIT-C <4 (median 35 years, IQR 24–50; $P < 0.001$). Likewise, participants with AUDIT-C $\geq$ 4 tended to have lower BMI (median 17.1 kg/m^2, IQR 15.3–18.9) than participants with AUDIT-C <4 (median 18.7 kg/m^2, IQR 16.3–21.3). Ever-smokers had significantly higher rates of unhealthy alcohol use than their counterparts (61% vs. 28%, $P < 0.001$). We also observed significant group-wise differences in alcohol use by education and employment, with higher use among the least educated (57%, $P < 0.001$) and among the unemployed (45% vs. 36%, $P < 0.01$). Finally, men with unhealthy alcohol use had a longer median duration of symptoms prior to treatment initiation (45 vs. 30 days, $P = 0.002$; Table 1).

Unfavorable outcomes

Overall, 198 (26%) participants experienced at least one unfavorable outcome, including 94 failures, 57 recurrences, and 76 deaths (Supplementary Table S1). Additionally, 43 (6%) men were LTFU. Median follow-up time was 15.8 months (IQR 6.1–18.7) from treatment initiation. The composite unfavorable outcome was observed at a rate of 23 per 100 py (95% CI 20–26); 31 per 100 py (95% CI 25–37) among men with unhealthy alcohol use vs. 18 (95% CI 14–22) among those with AUDIT-C <4 ($P \leq 0.001$). Of 76 men who died, 51 (67%) had unhealthy alcohol use, 21 (28%) died during treatment, and 24 (32%) failed treatment (Figure 1).

In our unadjusted analysis of baseline characteristics associated with unfavorable outcomes, we found that being severely underweight (IRR 2.00, 95% CI 1.35–2.97; $P = 0.001$), smoking (IRR 1.46, 95% CI 1.02–2.10; $P = 0.04$), having fewer than 5 years of education (IRR 3.66, 95% CI 2.14–6.26; $P \leq 0.001$), and living in poverty (IRR 1.97, 95% CI 1.22–3.19; $P = 0.01$) were risk factors (Supplementary Table S2).

Association of alcohol use with unfavorable outcomes

In our unadjusted analysis, unhealthy alcohol use was associated with the composite outcome (IRR 1.99, 95% CI 1.40–2.81; $P <0.001$), as well as with failure (IRR 1.92, 95% CI 1.24–2.96; $P = 0.003$) and death (IRR 2.88, 95% CI 1.69–4.91; $P < 0.001$). In our adjusted analysis, unhealthy alcohol use was a significant risk factor for the composite outcome (adjusted IRR [aIRR] 1.47, 95% CI 1.05–2.06; $P = 0.03$) and death (aIRR 1.90, 95% CI 1.08–3.34; $P = 0.03$) (Figure 2). The direction and magnitude of association was similar when LTFU was included as an outcome (Supplementary Table S3).

There was a dose-response relationship between AUDIT-C and the composite outcome (aIRR 1.06 per unit increment in AUDIT-C, 95% CI 1.01–1.10; $P = 0.01$). Higher AUDIT-C scores were also significantly associated with risk of TB recurrence specifically (aIRR 1.09 per unit increment in AUDIT-C, 95% CI 1.01–1.17; $P = 0.03$) (Figure 2, Figure 3).

Undernutrition was a significant effect modifier in the association between unhealthy alcohol use and unfavorable outcomes. Specifically, underweight men (BMI < 18.5 kg/m^2) with unhealthy alcohol use had more than two-fold increased risk of having unfavorable outcomes (aIRR 2.22, 95% CI 1.44–3.44; $P < 0.001$) compared to participants with both BMI $\geq$18.5 kg/m^2 and AUDIT-C <4. This group was also at significantly higher risk of TB recurrence (aIRR 2.25, 95% CI 1.02–4.96; $P = 0.04$) and death (aIRR 5.48, 95% CI 2.19–13.72; $P < 0.001$) relative to men with both BMI $\geq$ 18.5 and AUDIT-C <4. Severe undernutrition (BMI < 16.5 kg/m^2) was also a significant effect modifier (interaction term P value: 0.06) in the association between unhealthy alcohol use and unfavorable outcomes (aIRR 2.78, 95% CI 1.78–4.34; $P < 0.001$) and death (aIRR 8.58, 95% CI 3.73–19.70; $P < 0.001$) relative to men with both BMI $\geq$ 16.5 kg/m^2 and AUDIT-C <4 (Table 2).

DISCUSSION

Our study has several important findings. First, unhealthy alcohol use was highly prevalent and was identified in 40% of men with active TB. Second, unhealthy alcohol use was independently associated with higher risk of the composite unfavorable outcome and individually with all-cause mortality. The majority of deaths occurred prior to treatment completion and among men with unhealthy alcohol use. Finally, low BMI and unhealthy alcohol use had a combined

Table 1 Baseline characteristics of male TB patients by alcohol use

Baseline characteristics	Total ($n = 751$) n (%)*	AUDIT-C < 4 ($n = 449$, 60%) n (%)†	AUDIT-C ≥ 4 ($n = 302$, 40%) n (%)†	P value‡
Location				<0.001
Pune, India	581 (77)	382 (66)	199 (34)	
Chennai, India	170 (23)	67 (39)	103 (61)	
Type of residence				<0.001
Urban	598 (80)	378 (63)	220 (37)	
Rural	153 (20)	71 (46)	82 (54)	
Age, years				
Median [IQR]	39 [28–50]	35 [24–50]	42 [32–50]	<0.001
18–30	243 (32)	183 (75)	60 (25)	<0.001
30–50	343 (46)	165 (48)	178 (52)	
>50	165 (22)	101 (61)	64 (39)	
BMI, kg/m^2 (data missing, $n = 10$)				
Median [IQR]	17.9 [16.0–20.5]	18.7 [16.3–21.3]	17.1 [15.3–18.9]	<0.001
<16.5	243 (32)	120 (49)	123 (51)	<0.001
16.5–18.4	172 (23)	90 (52)	82 (48)	
18.5–24.9	285 (38)	195 (68)	90 (32)	
>25	41 (6)	36 (87)	5 (12)	
HIV (data missing, $n = 3$)§				0.51
Negative	727 (97)	436 (60)	291 (40)	
Positive	21 (3)	11 (52)	10 (48)	
Diabetes				0.30
No	507 (68)	296 (58)	211 (42)	
Yes	244 (32)	153 (63)	91 (37)	
Smoking				<0.001
None	481 (64)	344 (72)	137 (28)	
Ever	270 (36)	105 (39)	165 (61)	
Formal education, years				<0.001
<5	226 (30)	98 (43)	128 (57)	
5–10	358 (48)	215 (60)	143 (40)	
>10	167 (22)	136 (81)	31 (19)	
Employment (data missing, $n = 19$)				0.01
Unemployed	342 (46)	187 (55)	155 (45)	
Employed	389 (52)	248 (64)	141 (36)	
Monthly household income, INR (data missing, $n = 19$)				0.08
<5,000	113 (15)	58 (51)	55(49)	
5,000–10,000	312 (42)	182 (58)	130 (42)	
≥10,000	307 (41)	194(63)	113(37)	
Smear grade				0.01
Negative	225 (30)	154 (68)	71 (32)	
1+ or trace	279 (37)	159 (57)	120 (43)	
2+	147 (20)	75 (51)	72 (49)	
3+	100 (13)	61 (61)	39 (39)	
Culture- or Xpert-confirmed				<0.001
Negative	74 (10)	58 (78)	16 (22)	
Positive	677 (90)	391 (58)	286 (42)	
Symptom duration, days, median [IQR]	30 [20–60]	30 [20–60]	45 [21–90]	0.002

* Column-wise proportions used for total column.
† Row-wise proportions used to assess group-wise differences in alcohol use.
‡ Based on Fisher's exact test for categorical variables and Wilcoxon rank-sum test for continuous variables.
§ Individuals with HIV were eligible to enroll in the CTRIUMPh study but HIV was an exclusion criteria for the TBDM study.
AUDIT-C = Alcohol Use Disorders Identification Test-Concise; IQR = interquartile range; BMI = body mass index; INR = Indian rupee; CTRIUMPh = Cohort for TB Research by the Indo-US Medical Partnership; TBDM = Impact of Diabetes on TB Treatment Outcomes.

adverse effect. Thus, in our prospective cohort study where we were able to account for multiple comorbidities, we identified unhealthy alcohol use as an independent risk factor for unfavorable outcomes. Our results provide strong evidence of the devastating sequelae of alcohol use on TB treatment outcomes.

While most studies on alcohol and TB failed to use validated tools to ascertain alcohol use, there is consensus that alcohol use is high among patients with TB in India. In our cohort, the prevalence of unhealthy alcohol use was within the range reported in other studies from India (22–55%), but higher than the 20% observed in the United States and 32% in South Africa.[9–14,28,29] Based on our findings, alcohol use among male patients with TB is substantially higher than in the general population; 30% of men in India are estimated to consume alcohol compared to 54% in our study.[30]

Our results are consistent with the association between alcohol and unfavorable outcomes reported

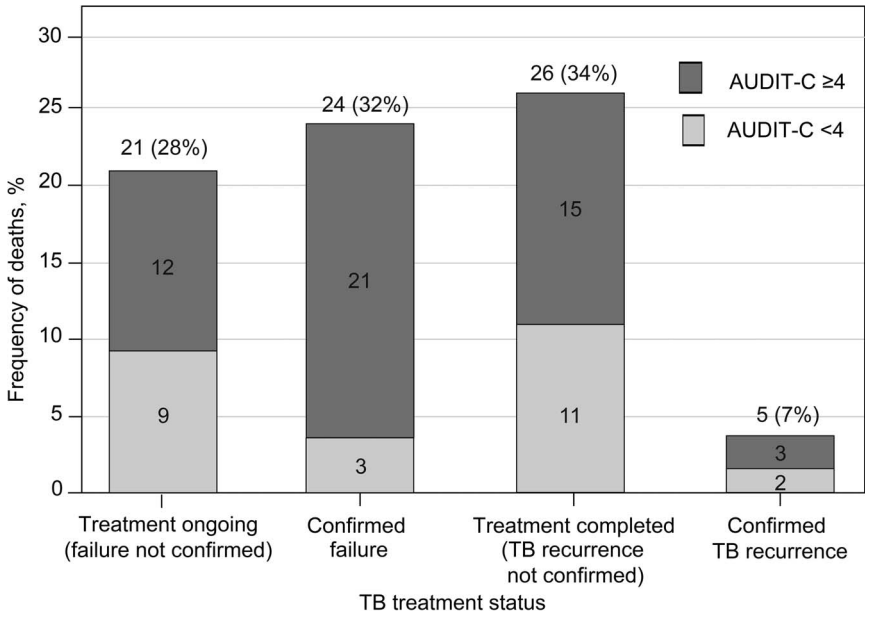

Figure 1 TB treatment status of male participants who died. Death was defined as all-cause mortality during TB treatment and up to 18 months post-treatment. Categories of TB treatment status are mutually exclusive: 1) "Treatment ongoing (failure not confirmed)" includes individuals who died before completing TB treatment (i.e., within 6 months of follow-up) and who did not have confirmation of treatment failure. 2) "Confirmed failure" includes individuals who tested positive for TB using smear or culture during the last 2 months of TB treatment before dying. 3) "Treatment completed (TB recurrence not confirmed)" includes individuals who died after successfully completing treatment and who did not have confirmation of TB recurrence. 4) "Confirmed TB recurrence" includes individuals who died after testing positive for TB using smear or culture following successful treatment completion. AUDIT-C = Alcohol Use Disorders Identification Test-Concise.

in recent systematic reviews, but we were able to offer stronger evidence by conducting a robust multivariable analysis in a TB-endemic setting. A recent review found that non-drinkers had increased odds of successful TB outcomes (9 studies; odds ratio [OR] 2.0, 95% CI 1.6–2.4). However, more than half of the studies included were rated low quality.[31] Similarly, Ragan et al. reported increased risk of death or treatment failure among patients with TB who used alcohol (12 studies; OR 2.55, 95% CI 1.77–3.66).[16] It should be noted that only two studies used high-quality alcohol definitions such as AUDIT-C, and only three were from TB-endemic countries. Furthermore, adjusted effect measures were rarely used. Using rigorous data collection and analytical methods, our study confirms that unhealthy alcohol use is independently associated with nearly a 50% increased risk of unfavorable outcomes.

Death was the only individual outcome independently associated with unhealthy alcohol use in our analysis. A recent systematic review concluded that unhealthy alcohol use was a major determinant of death among patients with TB, but primarily in low TB burden settings.[32] Our study extends evidence of this association to high TB burden settings, where interventions to reduce alcohol consumption are likely to have a significant public health benefit. Among men with unhealthy alcohol use who died in our cohort, about 40% had failed treatment. Nearly one third of deaths occurred post-treatment without evidence of TB recurrence. This may be explained by the fact that alcohol is a risk factor for all-cause mortality even in the general population.[33]

Although our analyses suggest that unhealthy alcohol use is reflective of other social determinants, it is a modifiable risk factor that could be addressed during TB treatment. A recent pilot study in South India showed that TB patients with alcohol use disorders who received individual counseling sessions had comparatively better outcomes.[14] Other approaches for integrating alcohol reduction interventions into TB care are being tested in India.[34]

There is evidence that undernourished patients with TB are at higher risk for TB treatment failure and death.[26,27] However, the combined effect of undernutrition and alcohol on TB treatment outcomes has not been well described. Addressing this gap in the literature is particularly important for low- and middle-income countries such as India, where 14.5% of the population is undernourished.[35] Our results offer clinically relevant evidence that male TB patients with both unhealthy alcohol use and low BMI are at significantly higher risk of unfavorable outcomes, specifically mortality. Checking AUDIT-C,

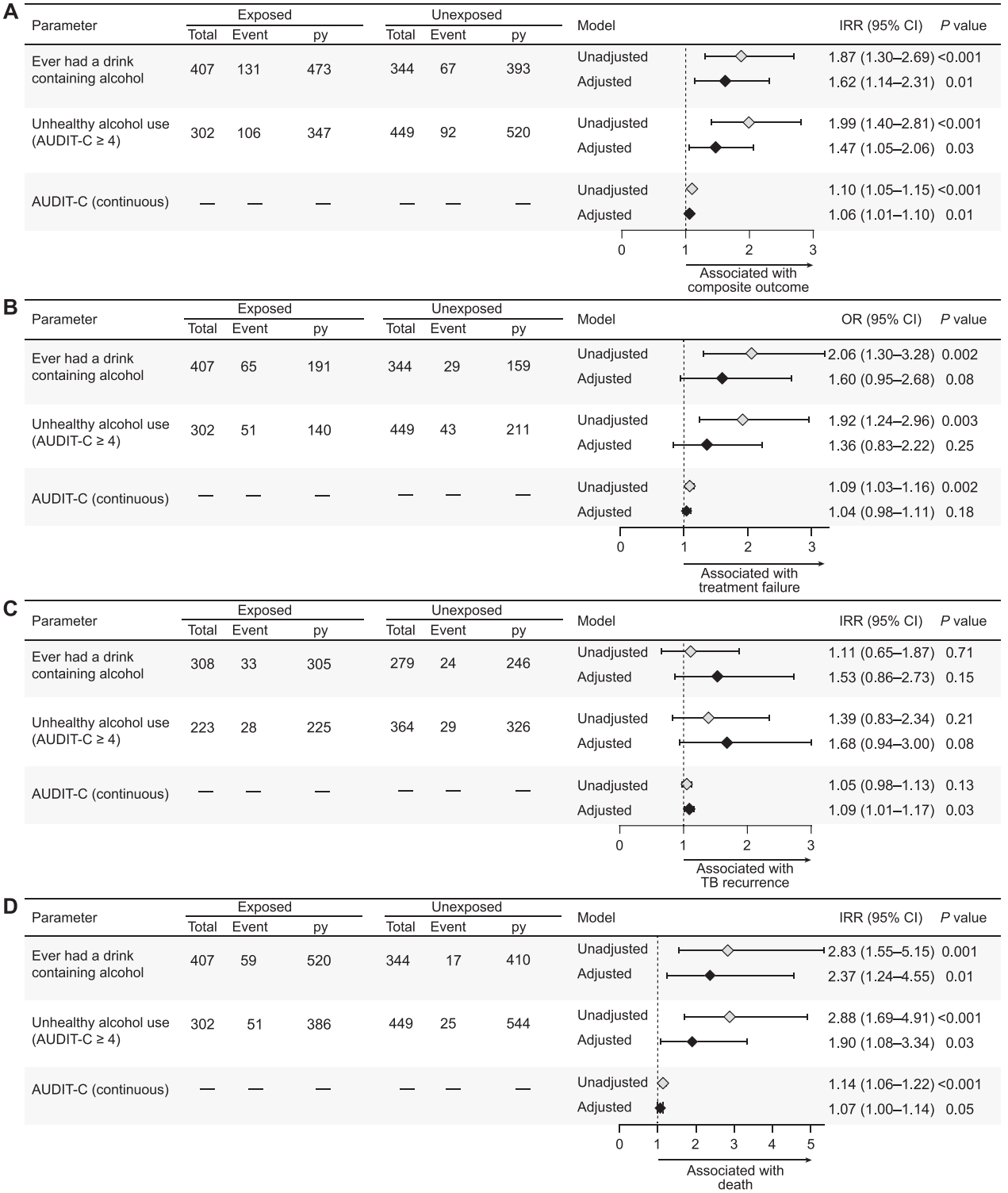

Figure 2 Forest plots of association of alcohol use with unfavorable TB treatment outcomes (adjusted)**. A)** "Composite" includes individuals who experienced treatment failure, TB recurrence, or death within 24 months of TB treatment initiation. **B)** "Treatment failure" defined as testing positive for TB using smear or culture during the last 2 months of TB treatment. **C)** "TB recurrence" defined as testing positive for TB using smear or culture following successful treatment completion. **D)** "Death" defined as all-cause mortality during TB treatment and up to 18 months post-treatment. A, B, C and D were adjusted for location, age, BMI, education, smoking, and smear grade. Multivariable negative binomial regression used for A, C, and D and multivariable logistic regression used for B. py = person-years; CI = confidence interval; AUDIT-C = Alcohol Use Disorders Identification Test-Concise; BMI = body mass index.

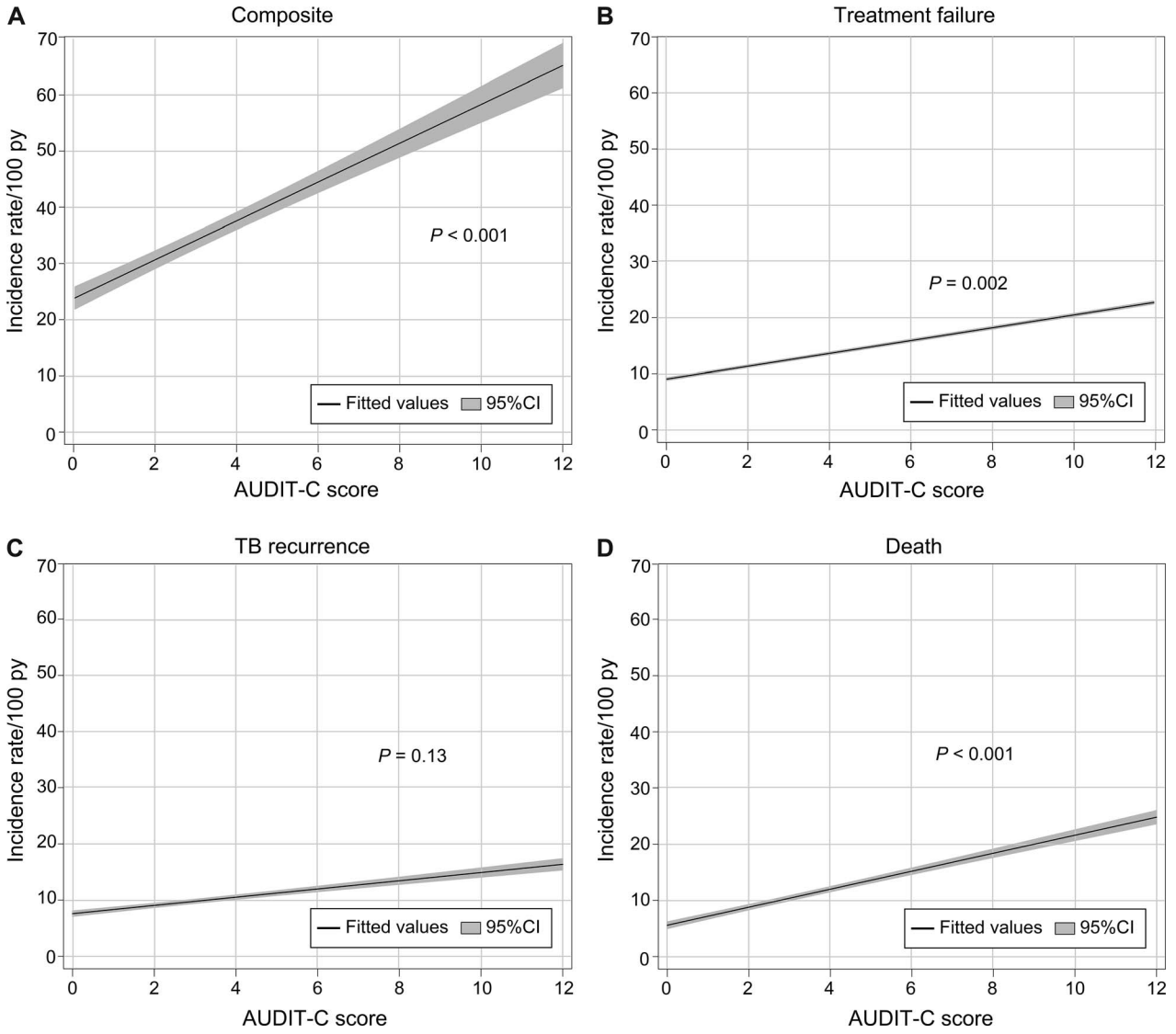

Figure 3 Dose-response relationship between AUDIT-C score and unfavorable TB treatment outcomes (unadjusted). **A)** "Composite" includes individuals who experienced treatment failure, TB recurrence, or death within 24 months of TB treatment initiation. **B)** "Treatment failure" defined as testing positive for TB using smear or culture during the last 2 months of TB treatment. **C)** "TB recurrence" defined as testing positive for TB using smear or culture following successful treatment completion. **D)** "Death" defined as all-cause mortality during TB treatment and up to 18 months post-treatment. The *y*-axis represents risk of outcome. py = person-years; CI = confidence interval; AUDIT-C = Alcohol Use Disorders Identification Test-Concise.

height and weight may be a simple screening tool at TB treatment initiation to identify high-risk patients in need of additional services, such as alcohol reduction counseling.

Our study has some limitations. First, we were not able to report detailed adherence data. Future studies should incorporate robust adherence measurements. Second, women were excluded from our analysis. However, in India less than 1% of women have alcohol-use disorders, and worldwide, women consistently use alcohol markedly less than men.[7] Third, we did not report on a few key comorbidities, such as HIV and mental health disorders. Finally, as our analysis was limited to baseline alcohol use among patients with drug-susceptible TB, we could not comment on patterns of alcohol use among MDR-TB patients. Despite these limitations, our study has several strengths. First, we analyzed data from well-characterized cohorts and conducted rigorous adjustment for confounding factors, which is generally lacking in the literature. Second, our overall sample size and exposure group was relatively large compared to other studies on this topic.[16] Finally, we pooled results across two cohorts within a programmatic setting in a TB-endemic country, enhancing generalizability of results.

CONCLUSIONS

The prevalence of unhealthy alcohol use among men with TB in India is high, and there is clear evidence

Table 2 Risk of unfavorable TB treatment outcomes among underweight participants with unhealthy alcohol use*

	Composite† IRR (95% CI)	*P* value	Treatment failure‡ OR (95% CI)	*P* value	TB recurrence§ IRR (95% CI)	*P* value	Death¶ IRR (95% CI)	*P* value
Underweight and unhealthy alcohol use								
BMI ≥ 18.5 + AUDIT-C < 4	Reference		Reference		Reference		Reference	
BMI ≥ 18.5 + AUDIT-C ≥ 4	1.12 (0.64–1.96)	0.69	0.62 (0.26–1.50)	0.29	1.98 (0.80–4.94)	0.14	2.04 (0.77–5.42)	0.15
BMI < 18.5 + AUDIT-C < 4	1.18 (0.75–1.86)	0.48	0.77 (0.39–1.50)	0.44	1.49 (0.68–3.26)	0.32	2.15 (0.88–5.24)	0.09
BMI < 18.5 + AUDIT-C ≥ 4	2.22 (1.44–3.44)	<0.001	1.68 (0.92–3.07)	0.09	2.25 (1.02–4.96)	0.04	5.48 (2.19–13.72)	<0.001
Severely underweight and unhealthy alcohol use								
BMI ≥ 16.5 + AUDIT-C < 4	Reference		Reference		Reference		Reference	
BMI ≥ 16.5 + AUDIT-C ≥ 4	1.20 (0.78–1.84)	0.40	0.99 (0.54–1.83)	0.98	1.76 (0.87–3.56)	0.12	2.00 (0.93–4.34)	0.08
BMI < 16.5 + AUDIT-C < 4	1.20 (0.74–1.97)	0.46	0.67 (0.32–1.41)	0.29	1.51 (0.69–3.29)	0.31	3.11 (1.28–7.57)	0.01
BMI < 16.5 + AUDIT-C ≥ 4	2.78 (1.78–4.34)	<0.001	1.76 (0.96–3.25)	0.07	2.15 (0.96–4.79)	0.06	8.58 (3.73–19.70)	<0.001

* Adjusted for location, age, education, smoking, and smear grade.
† Includes individuals who experienced treatment failure, TB recurrence, or death within 24 months of TB treatment initiation.
‡ Defined as testing positive for TB on smear or culture during the last 2 months of TB treatment.
§ Defined as testing positive for TB on smear or culture following successful treatment completion.
¶ Defined as all-cause mortality during TB treatment and up to 18 months post-treatment.
IRR = incidence rate ratio; CI = confidence interval; OR = odds ratio; BMI = body mass index; AUDIT-C = Alcohol Use Disorders Identification Test-Concise.

that unhealthy alcohol use adversely affects TB treatment outcomes. Specifically, compared to moderate or non-drinkers, male TB patients with unhealthy alcohol use are nearly two times more likely to die within 2 years of TB diagnosis. Those with both low BMI and unhealthy alcohol use are at highest risk of experiencing unfavorable outcomes. To improve TB treatment success and prevent premature death, alcohol reduction interventions are urgently needed and should be integrated into TB care in high-burden countries.

Acknowledgements

The authors would like to sincerely thank the study participants and study staff; and M B Arriaga-Gutierrez and B Andrade from the Multinational Organization Network Sponsoring Translational and Epidemiological Research (MONSTER) group who helped develop the figures.

This work was supported by the National Institute of Allergy and Infectious Diseases of the United States National Institutes of Health (Bethesda, MD, USA) [grant numbers #DAA3-18-64774-1 (CRDF Global), R01AI097494]; the Government of India's Department of Biotechnology for the CTRIUMPh Study as part of the Regional Prospective Observational Research for Tuberculosis (RePORT) India Consortium; and Persistent Systems (Pune, India) in kind.

The contents of this publication are solely the responsibility of the authors and do not represent the official views of the funders.

Conflicts of interest: none declared.

References

1 World Health Organization. Global tuberculosis report, 2020. Geneva, Switzerland: WHO, 2020.
2 Lönnroth K, et al. Alcohol use as a risk factor for tuberculosis - a systematic review. BMC Public Health 2008; 8: 289.
3 Imtiaz S, et al. Alcohol consumption as a risk factor for tuberculosis: meta-analyses and burden of disease. Eur Respir J 2017; 50(1): 1700216.
4 Simou E, Britton J, Leonardi-Bee J. Alcohol consumption and risk of tuberculosis: a systematic review and meta-analysis. Int J Tuberc Lung Dis 2018; 22(11): 1277–1285.
5 Revised National Tuberculosis Control Programme. National Strategic Plan for Tuberculosis Elimination 2017–2025. New Delhi, India: Central TB Division, Government of India, 2017.
6 Prasad R. Alcohol use on the rise in India. Lancet 2009; 373(9657): 17–18.
7 World Health Organization. Global status report on alcohol and health, 2018. WHO/MSD/MSB/18.2. Geneva, Switzerland: WHO, 2018.
8 World Health Organization. Global status report on alcohol and health, 2014. Geneva, Switzerland: WHO, 2014.
9 Veerakumar AM, et al. Alcohol use disorders among pulmonary tuberculosis patients under RNTCP in urban Pondicherry, India. Indian J Tuberc 2015; 62(3): 171–177.
10 Suhadev M, et al. Alcohol use disorders (AUD) among tuberculosis patients: a study from Chennai, South India, PLoS One 2011; 6(5): e19485.
11 Kolappan C, et al. Selected biological and behavioural risk factors associated with pulmonary tuberculosis. Int J Tuberc Lung Dis 2007; 11(9): 999–1003.
12 Thomas A, et al. Predictors of relapse among pulmonary tuberculosis patients treated in a DOTS programme in South India. Int J Tuberc Lung Dis 2005; 9(5): 556–561.
13 Santha T, et al. Risk factors associated with default, failure and death among tuberculosis patients treated in a DOTS

programme in Tiruvallur District, South India, 2000. Int J Tuberc Lung Dis 2002; 6(9): 780–788.
14 Thomas B, et al. Alcohol intervention strategy among tuberculosis patients: a pilot study from South India. Int J Tuberc Lung Dis 2017; 21(8): 947–952.
15 Thomas B, et al. Feasibility of an alcohol intervention programme for TB patients with alcohol use disorder (AUD)—a qualitative study from Chennai, South India. PLoS One 2011; 6(11): e27752.
16 Ragan EJ, et al. The impact of alcohol use on tuberculosis treatment outcomes: a systematic review and meta-analysis. Int J Tuberc Lung Dis 2020; 24(1): 73–82.
17 Bush K, et al. The AUDIT alcohol consumption questions (AUDIT-C): an effective brief screening test for problem drinking. Ambulatory Care Quality Improvement Project (ACQUIP). Alcohol use disorders identification test. Arch Intern Med 1998; 158(16): 1789–1795.
18 Gupte AN, et al. Cohort for Tuberculosis Research by the Indo-US Medical Partnership (CTRIUMPH): protocol for a multicentric prospective observational study. BMJ Open 2016; 6(2): e010542.
19 Mave V, et al. Prevalence of dysglycemia and clinical presentation of pulmonary tuberculosis in Western India. Int J Tuberc Lung Dis 2017; 21(12): 1280–1287.
20 Ministry of Health & Family Welfare, Government of India. Technical and operational guidelines for TB control in India. New Delhi, India: Central Tuberculosis Division, Ministry of Health & Family Welfare, GoI, 2016.
21 Nayak MB, et al. Detecting alcohol-related problems in developing countries: a comparison of 2 screening measures in India. Alcohol Clin Exp Res 2009; 33(12): 2057–2066.
22 Bradley KA, et al. Two brief alcohol-screening tests From the Alcohol Use Disorders Identification Test (AUDIT): validation in a female Veterans Affairs patient population. Arch Intern Med 2003; 163(7): 821–829.
23 Weir CB, Jan A. BMI classification percentile and cut off points. Treasure Island, FL, USA: StatPearls Publishing, 2020.
24 Ministry of Social Justice and Empowerment, Government of India. State-wise percentage of population below poverty line by social groups. New Delhi, India: GoI, 2018.
25 Stata. Stata 14 base reference manual. College Station, TX, USA: StataCorp, 2015; 1621–1633
26 Sinha P, et al. Undernutrition and tuberculosis: public health implications. J Infect Dis 2019; 219(9): 1356–1363.
27 Bhargava A, et al. Nutritional status of adult patients with pulmonary tuberculosis in rural central India and its association with mortality. PLoS One 2013; 8(10): e77979.
28 Volkmann T, et al. Tuberculosis and excess alcohol use in the United States, 1997-2012. Int J Tuberc Lung Dis 2015; 19(1): 111-9.
29 Peltzer K, et al. Hazardous and harmful alcohol use and associated factors in tuberculosis public primary care patients in South Africa. Int J Environ Res Public Health 2012; 9(9): 3245-57.
30 International Institute for Population Sciences. India National Family Health Survey (NFHS-4), 2015–16. Mumbai, India: IIPS and ICF, 2017.
31 Chaves Torres NM, et al. Factors predictive of the success of tuberculosis treatment: A systematic review with meta-analysis. PLoS One 2019; 14(12): e0226507.
32 Waitt CJ, Squire SB. A systematic review of risk factors for death in adults during and after tuberculosis treatment. Int J Tuberc Lung Dis 2011; 15(7): 871-85.
33 GBD 2016 Alcohol Collaborators. Alcohol use and burden for 195 countries and territories, 1990–2016: a systematic analysis for the Global Burden of Disease Study 2016. Lancet 2018; 392(10152): 1015–1035.
34 National Institutes of Health. Alcohol reduction among people with TB and HIV in India (HATHI): US National Library of Medicine, 2020. https://clinicaltrials.gov/ct2/show/NCT04230395.
35 Development Initiatives. 2020 Global Nutrition Report: action on equity to end malnutrition. Bristol, UK: Development Initiatives, 2020.

RÉSUMÉ

CONTEXTE : Environ 10% des cas de TB dans le monde sont attribuables à l'alcool. Les preuves associant l'alcool à un mauvais résultat du traitement de la TB sont faibles.

MÉTHODE : Nous avons évalué prospectivement des hommes (≥18 ans) atteints de TB pulmonaire en Inde pendant une durée allant jusqu'à 24 mois afin de rechercher l'association entre consommation d'alcool et résultats du traitement. Une consommation abusive d'alcool a été définie comme un test de « Alcohol Use Disorders Identification » (AUDIT-C) ≥ 4 à l'entrée. Les résultats défavorables du traitement ont inclus l'échec, la rechute et le décès toutes causes confondues, analysées comme paramètres composites et indépendants.

RÉSULTATS : Parmi 755 hommes, nous avons identifié un abus d'alcool chez 302 (40%). L'âge médian était de 39 ans (IQR 28–50), 414 (55%) étaient maigres (indice de masse corporelle [IMC] < 18,5 kg/m^2) et 198 (26%) ont eu un résultat défavorable. L'abus d'alcool a été un facteur de risque indépendant de résultats composites défavorables (taux d'incidence ajusté [IRRa] 1,47 ; IC 95% 1,05–2,06 ; $P = 0{,}03$) et décès (IRRa 1,90 ; IC 95% 1,08–3,34 ; $P = 0{,}03$), spécifiquement. Nous avons trouvé une interaction significative entre AUDIT-C et IMC ; les hommes amaigris ayant une consommation abusive d'alcool avaient un risque accru de résultats défavorable (aIRR 2,22 ; 95% CI 1,44–3,44 ; $P < 0{,}001$) comparés aux hommes ayant un IMC > 18,5 kg/m^2 et un AUDIT-C < 4.

CONCLUSION : L'abus d'alcool a été indépendamment associé à des résultats défavorables du traitement de la TB ce qui met l'accent sur le besoin d'intégrer des interventions efficaces relatives à l'alcool dans la prise en charge de la TB.